ASYMPTOMATIC BACTERIURIA

IN OLDER

DIABETIC WOMEN

A Dissertation submitted in part fulfillment of M.D. Branch-1

(General Medicine) examination of the Tamil Nadu

Dr. M.G.R. Medical University, Chennai to be held on

March 2009.

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CERTIFICATE

This is to certify that the dissertation entitled ***"Asymptomatic Bacteriuria in older diabetic women"*** is the bonafide original work of Dr. Sushil Thomas Alexander towards the M.D. Branch-1 (General Medicine) Degree Examination of the Tamil Nadu Dr. M.G.R University, Chennai to be conducted in 2009.

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CONTENTS

1. INTRODUCTION

India has become “the diabetes capital of the world” [1] and diabetes and its attendant complications are on the increase. Diabetic patients have an increased risk of getting infections especially urinary tract infections and asymptomatic bacteriuria is one of the leading forerunners to urinary tract infection.[2,3,4]

Patients with diabetes have an increased risk of urinary tract infections [5,6]. There is a roughly fivefold greater propensity toward urinary tract infections in diabetic women [7]. Urinary tract infections are likely to be more severe in diabetic than nondiabetic women in terms of the complications involved [25] .Whether symptomatic urinary tract infections are preceded by asymptomatic bacteriuria (ASB) is a matter of debate .[3,8,9]

Diabetic women have a higher prevalence of asymptomatic bacteriuria as compared to men and the prevalence has been found to increase with age. Most of the studies done on this condition have been in Europe and North America[11] and there are hardly any studies reported from India looking at the prevalence and associated risk factors for asymptomatic bacteriuria in the elderly diabetic population.

The general recommendation is that asymptomatic bacteriuria is not to be treated[12,13,14,15] and that screening for this condition and its treatment is necessary only in pregnant women and people undergoing urethral procedures with a risk of mucosal injury . There are studies which show people with asymptomatic bacteriuria have a higher risk for subsequent urosepsis.[4,16]

Hence this study was done among the diabetic out-patient population of a tertiary teaching care hospital in South India with a view of looking at potentially modifiable risk factors including cystopathy and bladder outlet obstruction to reduce the overall risk posed by this condition.

2. AIMS AND OBJECTIVES OF THE STUDY

AIM

To study the prevalence and the clinical and the laboratory predictors of asymptomatic bacteriuria in older diabetic women.

OBJECTIVE

A) To estimate the prevalence of asymptomatic bacteriuria in elderly diabetic women.

B) To assess if obstructive uropathy / diabetic cystopathy has an association with asymptomatic bacteriuria in older diabetic women.

C) To assess if other clinical and laboratory factors such as $HbA_{1C,}$ duration of diabetes, body mass index etc have an association with asymptomatic bacteriuria in older diabetic women.

3. REVIEW OF LITERATURE

1. EPIDEMIOLOGY OF DIABETES MELLITUS

The prevalence of diabetes mellitus in India has been growing by leaps and bounds[17,18] . In the last twenty years there has been a three fold increase in the prevalence of diabetes [19,20] .The population of India is now more than 1000 million and the estimate of the actual number of diabetics in India is around 40 million[21]. India's diabetic population now ranks first in the world, even ahead of China although China's total population is higher. This is because the prevalence of diabetes is far higher in India. It is estimated that by the year 2010 India will have nearly 20% of the world's diabetic population[1]. After a 10 to 15 years period of diabetes, the prevalence of all diabetes related complications increases markedly. The figure 1 below shows the estimated number of diabetic subjects in India.[19,20]

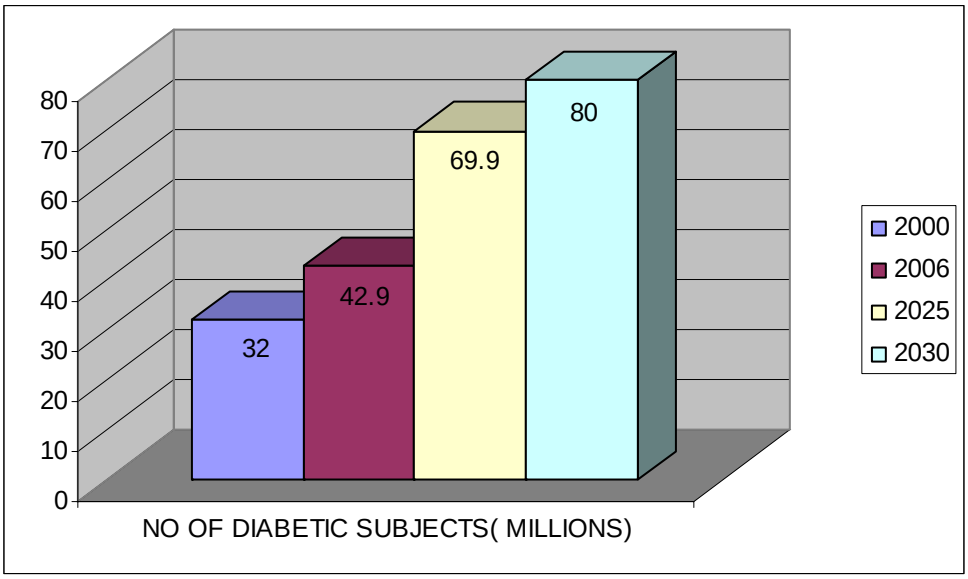

Figure1: Indian diabetic population

2. DIAGNOSIS OF DIABETES MELLITUS

A diagnosis of Diabetes mellitus can be made, according to American Diabetes Association (ADA) 2007 guidelines, if the blood sugar values fulfill any one of the following criteria[22] :-

ADA Criteria for the diagnosis of diabetes

1. Symptoms of diabetes and a casual plasma glucose >/=200 mg/dl (11.1 mmol/l).
Casual is defined as any time of day without regard to time since last meal. The classic symptoms of diabetes include polyuria, polydipsia, and unexplained weight loss.
OR

2. FPG >/=126 mg/dl (7.0 mmol/l). Fasting is defined as no caloric intake for at least 8 h.
OR

3. 2-h plasma glucose >/=200 mg/dl (11.1 mmol/l) during an OGTT.
The test should be performed as described by the World Health Organization, using a glucose load containing the equivalent of 75-g anhydrous glucose dissolved in water.

Diagnosis of Impaired Fasting glucose
Fasting glucose >100mg/dl and <126mg/dl

Diagnosis of Impaired glucose tolerance
2 hours postprandial glucose >140mg/dl and <200mg/dl.

The 75 gm OGTT is more sensitive, more specific than fasting plasma glucose in diabetes but is poorly reproducible and rarely performed in practice.

3. URINARY TRACT INFECTIONS IN DIABETES MELLITUS

Patients with diabetes have an increased risk of infections[23, 24] with the urinary tract being the most prevalent infection site [5, 6]. There is a roughly fivefold greater propensity toward urinary tract infections in diabetic women [7]. Urinary tract infections are likely to be more severe in diabetic than nondiabetic women in terms of the complications involved [26] .Many urinary tract infections are asymptomatic and whether symptomatic urinary tract infections are preceded by asymptomatic bacteriuria (ASB) is a matter of debate [3, 8, 9] .

4. ASYMPTOMATIC BACTERIURIA

Half a decade ago routine quantitative urine culture for the microbiological diagnosis of urinary tract infections was done by Kass and other investigators.[10,26,138] Widespread acceptance and application of the quantitative urine culture identified several patient populations who were clinically asymptomatic but had a high prevalence of positive urine cultures [27] These included pregnant women, individuals with urological abnormalities, patients with indwelling urethral catheters, elderly individuals and diabetics. The prevalence of asymptomatic bacteriuria varies in different age groups and also population groups. It is higher in the older population, non ambulant people, people with indwelling urinary catheters and people practicing intermittent clean self catheterisation .The values of prevalence in different people groups are shown in the table in the next page.

Table 1. Prevalence of Asymptomatic bacteriuria in selected populations

Population	**Prevalence (%)**
Healthy premenopausal women[28]	1.0 to 5.0
Pregnant women[28]	1.9 to 9.5
Post menopausal women(50-70 years) [28]	2.8 to 8.6
Patients with diabetes	
Women[13]	9.0 to 27.0
Men[13]	0.7 to 1.0
Older community dwelling patients	
Women (> 70 years) [28]	>15.0
Men[13]	3.6 to 19.0
Older long- term care residents	
Women[13]	25.0 to 50.0
Men[13]	15.0 to 40.0
Patients with spinal cord injuries	
Intermittent catheter[29]	23.0 to 89.0
Sphincterotomy and condom catheter[30]	57.0
Patients undergoing haemodialysis[31]	28.0
Patients with indwelling catheter	
Short term[32]	9.0 to 23.0
Long term[32]	100

5. DEFINITION OF ASYMPTOMATIC BACTERIURIA

Asymptomatic bacteriuria also referred to as asymptomatic urinary tract infection[28] is defined as the presence of at least 10^5 colony-forming units (cfu)/ml of one or two bacterial species in a clean-voided midstream urine sample from individuals without symptoms of a urinary tract infection.

According to Infectious Disease Society of America guidelines 2005 [33] the diagnosis of asymptomatic bacteriuria in women is appropriate only if the same species is present in quantities of at least 10^5 cfu/mL of urine in at least two consecutive voided specimens. Alternative definitions have been used in some studies. Bacteriuria has been identified with only a single specimen [2], or requiring as many as three consecutive specimens with consistent microbiological results[34]. Studies that define bacteriuria with only a single voided specimen report a higher prevalence of asymptomatic bacteriuria then those requiring persistent bacteriuria from two or more specimens. For men, a single voided specimen with a quantitative count of a potential uropathogen of >/= 10^5 cfu/mL is sufficient to diagnose bacteriuria[35]

For any asymptomatic patient, bacteriuria is also defined as a single catheterized urine specimen with one bacterial species isolated in counts >/= 10^2 cfu/ml. Though a count of >/= 10^2 cfu/ml has been validated in research settings to be significant, many clinical laboratories do not routinely quantify counts in these range.

6. SCREENING FOR ASYMPTOMATIC BACTERIURIA

Unless the person is symptomatic screening for asymptomatic bacteriuria is not recommended except in the second trimester of pregnancy (12-16 weeks gestation) [36] or if the person needs to undergo an urological procedure with risk of having a mucosal injury. The Infectious Disease Society of America Guidelines 2005 recommendations for asymptomatic bacteriuria in adults are summarized in the table 2 and 3 below.[33]

Table 2. IDSA Recommendations for screening for, and treatment of, asymptomatic bacteriuria (ASB) 33

Recommendation	Grade
Pregnant women should be screened for bacteriuria by urine culture at least once in early pregnancy, and they should be treated if the results are positive	A-I
Screening for ,and treatment of ,ASB before transurethral resection of the prostrate is recommended	A-I
Screening for ,and treatment of ,ASB is recommended before other urological procedures for which mucosal bleeding is anticipated	A-III

Table 3. IDSA Recommendations against screening for, and treatment of, asymptomatic bacteriuria 33

Recommendation	Level
1.Premenopausal ,non pregnant women	A-I
2.Diabetic women	A-I
3.Older people living in the community	A-II
4.Elderly,institutuionalized people	A-I
5.People with spinal-cord injury	A-I
6.Patients with indwelling catheters	A-I

Strength of recommendation

'A' means the recommendation is always valid.

'B' that it is valid in most cases.

'C' it may or may not be appropriate.

Quality of evidence is judged by Roman Numericals.

'I' for at least one prospective randomized comparative trial.

'II' for prospective cohort studies or case control studies.

'III' for consensus of experts in the absence of appropriate clinical trials.

7 .SCREENING TESTS FOR ASYMPTOMATIC BACTERIURIA

Other tests for asymptomatic bacteriuria which have been used for screening purposes are:

1. Nitrite test

2. Leukocyte esterase test.

Urinary nitrite tests for asymptomatic bacteriuria have 43% sensitivity and 99% specificity. Urinary leukocyte esterase test for asymptomatic bacteriuria has 77% sensitivity and 96% specificity. Screening tests for asymptomatic bacteriuria using both nitrite and leukocyte esterase tests combined have 92% sensitivity and 95% specificity. [37,38]

8. PATHOPHYSIOLOGY OF ASYMPTOMATIC BACTERIURIA

The presence of bacteria in the absence of a major inflammatory response points to a subtle disturbance of the host –parasite interaction[39]. The microbiology of asymptomatic bacteriuria is similar to that of cystitis and pyelonephritis .Some bacterial strains with reduced capability for fimbrial expression appear to have the capability of relatively rapid growth thus causing asymptomatic bacteriuria. [40] Alternatively strains implicated in asymptomatic bacteriuria may be less virulent and therefore may not necessarily be true pathogens[41, 42, 43]. Potential host factors may also be responsible for the absence of symptoms. A study of children with asymptomatic bacteriuria demonstrated lower levels of neutrophil Toll –like receptor

(TLR4) expression compared to age matched controls.[44] One study in which granulocyte function was tested in women with diabetes and asymptomatic bacteriuria found no difference in function as compared to non bacteriuric and healthy control subjects. [45]

The bacteriology of asymptomatic UTI is similar in diabetic and nondiabetic women with the preponderance being caused by Escherichia coli and other gram-negative organisms.

9. CONSEQUENCES OF ASYMPTOMATIC BACTERIURIA IN DIABETES MELLITUS

Asymptomatic bacteriuria in diabetes mellitus identifies a group at risk for subsequent severe urinary tract infections [16,46,47] .In one study a large cohort of diabetic women in the Netherlands was studied to determine the incidence of symptomatic UTIs [4] .In women with type 2 diabetes (but not with type 1), the presence of asymptomatic bacteriuria at baseline increased the risk of subsequent symptomatic UTI in the 18 month follow-up period from 19 to 34 percent. The rate of asymptomatic bacteriuria in this population was approximately 28 percent. By contrast, incidence of asymptomatic UTI was 6 percent in women who were not diabetic but attended other clinics in the same institution [11].

In another prospective observational study 496 adults with type 1 or 2 diabetes were followed for 2.9+/-0.6 years for hospital admission for/with urosepsis or death.

Of them thirty-six patients (7.3%) had ASB, comprising 33 females (14.4% of all females) and three males (1.1% of all males). Only female sex predicted ASB amongst a range of variables including indices of metabolic control. Twenty-nine patients (5.8%) were subsequently hospitalized with urosepsis. Of these, urosepsis was the principal diagnosis in 12 (41%).Diabetics with ASB were 4.4 times more likely to be hospitalized with urosepsis as principal diagnosis as compared to diabetics without ASB (hazard ratio 4.4[95% CI] [1.2-16.5]; p=0.004).

Thus the presence of ASB identifies a group of diabetic patients who are at significantly increased risk of subsequent urosepsis requiring hospitalization. However there is a consensus that in the absence of anatomical or functional abnormalities of the urinary tract, ASB per se does not lead to renal scarring, renal dysfunction, or hypertension[48]. A 14 year follow up of asymptomatic and symptomatic diabetic patients was done to look at the natural history of untreated asymptomatic bacteriuria .It was found that the clinical symptoms of acute pyelonephritis occur with similar frequency in both groups and there was no deterioration of kidney function was found and the occurrence of arterial hypertension did not differ significantly in both groups at the beginning and end of the follow-up.[49]

10. RISK FACTORS FOR ASYMPTOMATIC BACTERIURIA

A prospective study which evaluated 796 sexually active, nonpregnant women from 18 through 40 years of age over a period of six months for the occurrence of asymptomatic bacteriuria concluded that asymptomatic bacteriuria was associated with the same risk factors as for symptomatic urinary tract infection, particularly the use of a diaphragm plus spermicide and sexual intercourse[2].

Genetic factors may also be involved. One Canadian study showed a higher rate of asymptomatic UTI in aboriginal diabetic women than in diabetic women of European heritage [50]

In Type 2 Diabetes Factors that have correlated with asymptomatic bacteriuria are female sex, urinary incontinence, leukocyturia, and elevated C reactive protein concentration. [47,51]

A prospective cohort study of 218 diabetic and 799 nondiabetic postmenopausal women examined risk factors for asymptomatic bacteriuria and UTI [51.] Increased risk occurred mainly in women taking insulin (relative risk 3.7) and those with a longer diabetes duration (>10 years, relative risk 2.6) but not in those with poor glucose control. Women with diabetes and bacteriuria are characterized by a more prolonged duration of diabetes and long-term complications such as neuropathy, but not by abnormal parameters of diabetic control, such as glycosylated haemoglobin. [50]

It has not been universally agreed that asymptomatic bacteriuria poses risks. In another study in order to compare the incidence of symptomatic UTI in diabetic patients with and without asymptomatic bacteriuria (ASB), and to identify other

risk factors for these infections, 289 females and 168 males were studied over a 12-month period[52]. Symptomatic UTI occurred in 69.2% of patients with ASB (67.6% female and 76.5% male) versus 9.8% without ASB (14.9% female and 2.6% male). ASB and urinary incontinence were associated with symptomatic UTI in both women and men. Other risk factors included previous antimicrobial treatment and macrovascular complications in women and obesity and prostatic syndrome in men. The presence of ASB was found to be the major risk factor for developing symptomatic urinary tract infection.

11. ASYMPTOMATIC BACTERIURIA IN DIABETIC WOMEN

Asymptomatic bacteriuria may be considered as a complication in women with diabetes[11]. In contrast with men, a higher incidence of asymptomatic bacteriuria has been found in women with diabetes than women without the disease. [6,8,9,53,54,141]

The relevance of asymptomatic bacteriuria in diabetic women stems from the following factors:

There is a roughly fivefold greater propensity toward urinary tract infections in diabetic women [7]. Urinary tract infections are likely to be more severe in diabetic than nondiabetic women in terms of the complications involved [25] . Asymptomatic bacteriuria often precedes symptomatic urinary tract infections in type 2 diabetes. [3] The best estimate is an approximately three- to fourfold increase in risk of

asymptomatic bacteriuria in diabetic women compared to non diabetic women (18 versus 6 percent [50], 26 versus 6 percent [55].

12 .ASYMPTOMATIC BACTERIURIA IN THE ELDERLY POPULATION

Asymptomatic bacteriuria in the elderly is associated with a significant proneness to infection[56.] One study showed it was associated with a reduction in survival of 30 to 50 per cent.[57]The prevalence of ASB in the elderly ranges from 17 to 50 % in women, and 6-34% in men. It increases with advancing age and the level of disability. Elderly people living at home are less likely to have bacteriuria than those living in long term care facilities .In the absence of urinary obstruction, ASB in the elderly does not lead to renal failure or hypertension.

Majority of studies done show that there is no role for screening for or treatment of asymptomatic bacteriuria among older persons in the community[33] as these patients are not at increased risk for adverse outcomes related to asymptomatic bacteriuria[29,58-62]. This was also brought out in a randomized controlled trial of antibiotic therapy for 124 elderly ambulatory women with asymptomatic bacteriuria [58.] There was no significant difference in the number of symptomatic episodes during the six-month follow-up period. In addition, bacteriuria is transient and tends to recur after therapy, with emergence of antibiotic resistance [33].

There is also no role for screening for or treatment of asymptomatic bacteriuria among the elderly in health care facilities [33]. Although half of women and 15 to 40 percent of men have asymptomatic bacteriuria [29], antimicrobial treatment has not been shown to be of benefit. This was illustrated in a study of 191 nursing home residents with incontinence and bacteriuria who were randomly assigned to immediate or delayed treatment [63]. Eradicating bacteriuria had no short-term effects on the severity of chronic urinary incontinence. In addition, bacteriuria tends to recur after therapy, with emergence of antibiotic resistance.

In conclusion attempts to obtain sterile urine in the elderly with prolonged antimicrobial treatments appear to be futile due to high rates of infection. In addition, no differences in morbidity and mortality were seen when antimicrobial therapy was given. Thus in the absence of urological abnormalities, ASB is a benign condition that does not require antibiotic treatment.

13. ASYMPTOMATIC BACTERIURIA AND OBSTRUCTIVE UROPATHY

Is obstructive uropathy associated with higher incidence of asymptomatic bacteriuria? There is a paucity of literature or studies regarding this association. Such studies would be relevant due to the high prevalence of obstructive uropathy among the elderly and also especially in long term diabetics.

14. PYURIA AND ASYMPTOMATIC BACTERIURIA

Pyuria is often a common accompaniment of asymptomatic bacteriuria. The presence of asymptomatic bacteriuria and pyuria varies in different population groups. Pyuria is accompanied by a greater prevalence of asymptomatic bacteriuria.

Pyuria causes an increased prevalence of asymptomatic bacteriuria but has no prognostic significance and hence should not influence decisions about antimicrobial therapy. [64-66]

Table 4. Prevalence of ASB in different populations with or without pyuria.

Population	ASB(%) in patients without pyuria	ASB (%) in patients with pyuria
Healthy adult women[2]	2--5	32
Pregnant women[67]	2--11	50
Diabetic women[50]	7--9	70
Elderly : nursing home[29]	5--50	90
Spinal cord injury patients[30]	50	33--86
Indwelling urethral catheter[68]	100	70

15. GUIDELINES FOR THE TREATMENT OF ASYMPTOMATIC BACTERIURIA

A common dilemma in clinical medicine is whether to treat asymptomatic patients who present with bacteria in their urine[140]. Several studies have shown that, while treatment of asymptomatic bacteriuria is effective in eliminating the bacteria from the urine, the benefit does not persist. Thus antibiotic therapy does not reduce subsequent reinfection causing asymptomatic bacteriuria [69.] Moreover treatments with antibiotics have increased the incidence of resistant organisms which are more dangerous. Treating asymptomatic bacteriuria in diabetic women is not recommended based upon multiple studies which have not demonstrated improved outcomes with therapy[139].

The best data come from a prospective trial in which 105 diabetic women over the age of 16 years with asymptomatic bacteriuria were randomly assigned to 14 days of antibiotics or placebo[12.] At four weeks after the end of therapy, a significantly greater proportion of patients in the antibiotic group cleared the bacteriuria (80 versus 22 percent with placebo). After this six week period, the group assignment was revealed, and patients were followed for a mean of 27 months; bacteriuria was assessed at three month intervals and patients who originally received antibiotics were treated during subsequent episodes. Patients were also evaluated for symptomatic UTI, pyelonephritis, and hospitalization for UTI. There were no significant differences between the groups in the development of a symptomatic UTI, the timing of onset of such an infection or any of the other parameters.

Patients in the antibiotic treatment group had nearly five times the number of days on antibiotics compared to the placebo group. However, as in the subgroups described above, antibiotic therapy for asymptomatic bacteriuria does not affect the frequency of or time to symptomatic infection (including pyelonephritis), reinfection is common, and long-term prognosis is not improved. [12-15]

16. UROLOGICAL COMPLICATIONS OF DIABETES MELLITUS

Diabetes and urological diseases are very common health problems that markedly increase in prevalence and incidence with advancing age [70-72]. Diabetes is associated with an earlier onset and increased severity of urologic diseases, resulting in costly and debilitating urologic complications. Urologic complications including bladder dysfunction, sexual and erectile dysfunction, as well as urinary tract infections, have a profound effect on the quality of life of women with diabetes.[73]

Over 50% of men and women with diabetes have bladder dysfunction [74, 75]. Diabetes has been identified as an important independent risk factor for incontinence in several large observational studies, including the Nurses' Health Study, and is associated with 30–100% increased risk[76-79.] Other aspects of diabetes severity, including glycaemic control and microvascular complications resulting in damage to innervation of the bladder, have been suggested as possible mechanisms for increasing incontinence [80]. Questions remain as to whether there is any association between bladder dysfunction and urinary incontinence in relation to asymptomatic bacteriuria in diabetics. The methods used to document the

urological associations of asymptomatic bacteriuria in diabetics include uroflowmetry and post voidal residual urine and urodynamic studies.

17. UROFLOWMETRY

Uroflowmetry is the study of the flow of the urine from the urethra[81.] It is the noninvasive determination of the characteristics of urine flow. Urine flow is described in terms of rate and pattern and may be continuous or intermittent[82]

Urinary flow rate determined is thus the product of the final result of the act of voiding and is influenced by the variables - detrusor pressure, urethral patency and sphincter relaxation. Because all three variables influence the uroflow, uroflometry cannot be used to establish a diagnosis, but, when combined with measurement of residual urine it provides a rapid and economic screening tool for the effectiveness of the act of voiding. Patients with abnormal uroflow require more detailed evaluation to further elucidate the cause of their voiding problem.

The patient who presents for an uroflowmetry study should be well hydrated with a reasonably full bladder. An overly distended bladder may cause temporary detrusor compensation resulting in a lower than normal flow rate. The study should be performed in relative privacy and the patient should be encouraged to void in as normal a fashion as possible. It is important to obtain a flow that is representative of the patients' usual flow and the patient should be asked about this .If there is any doubt the test should be repeated [82].

The normal uroflow curve is plotted with the flow rate on the Y axis (ml/sec) and time on the x axis (sec). The precise shape of the flow curve is decided by

detrusor contractility, the presence of any abdominal straining and by the bladder outlet. [83]

The flow pattern that is the shape of the flow tracing can sometimes be used to make a presumptive diagnosis although it cannot be used to make a definitive diagnosis. The normal flow pattern is a continuous bell shaped smooth curve with a rapidly increasing flow rate. An intermittent flow pattern is one that has one or several episodes of flow increasing or decreasing (or ceasing completely) and is more commonly secondary to abdominal straining or external sphincter spasm (e.g. detrusor sphincter dyssynergia).The typical obstructed flow pattern has a plateau-shaped curve with a prolonged flow time ,sustained low flow state and increased time to Qmax. But this is not diagnostic of outlet obstruction because detrusor hypocontractility can have a similar tracing.

The International Continence Society has recommended the following definitions for the evaluation of uroflometry [84.]

Flow rate is defined as the volume of fluid expelled via the urethra per unit time. It is expressed in ml/s. The normal flow rate from a full bladder is about 20-25 mL/s in men and 25-30 mL/s in women. These variations are directly related to the volume voided and the person's age. Obstruction should be suspected in any adult voiding with a full bladder at a rate of less than 15 mL/s. A flow rate less than 10 ml/s is considered definite evidence of obstruction. Lower flow rates suggest bladder outlet obstruction or weak detrusor contractility [85] .Moreover a

normal flow maybe seen in patients with urethral obstruction if they generate detrusor pressure high enough to overcome the increased urethral resistance.[86]To distinguish between obstruction and impaired detrusor contractility it is necessary to measure detrusor pressure and uroflow simultaneously[64,85,88-90]

Table 5.Utility of Maximal urinary flow rate (Qmax) for diagnosis of bladder outlet obstruction [91]

	Threshold Q max (ml/sec)	
	<10	**<15**
Sensitivity	47%	82%
Specificity	70%	38%
Positive predictive value	70%	67%
1-negative predictive value	54%	42%

Higher flow rates suggest bladder spasticity or excessive use of abdominal muscles to assist voiding. Intermittent flow patterns generally reflect spasticity of the sphincter or straining to overcome resistance in the urethra.

Some of the terminologies used in urodynamics and lower urinary tract symptoms are shown in Figure2:

Voided volume is the total volume of urine expelled through the urethra.

Maximum flow rate (Q max) is the maximum measured value of the flow rate (the peak of the flow curve) after correction for artifacts

Voiding time is total duration of micturition, i.e. includes interruptions. When voiding is completed without interruption, voiding time is equal to flow time.

Flow time is the time over which measurable flow actually occurs.

Average flow rate is voided volume divided by flow time. The average flow should be interpreted with caution if flow is interrupted or there is a terminal dribble.

Time to maximum flow is the elapsed time from onset of flow to maximum flow.

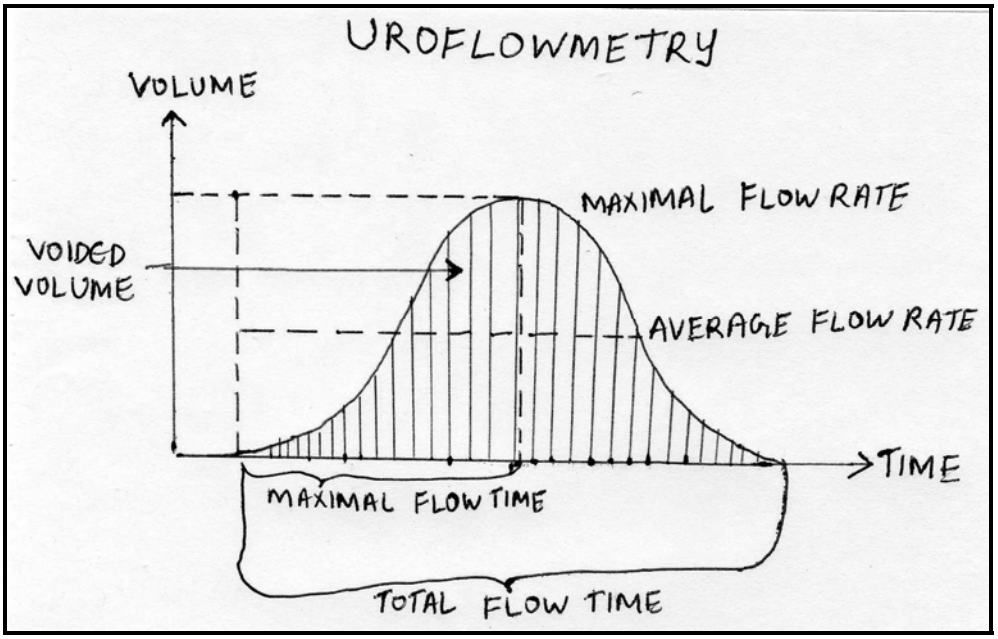

Figure 2. Graphical representation of uroflowmetry

Peak flow rate is generally the most reliable in detecting abnormal voiding.

It is influenced by several factors.

1. Age and sex.

In men, Qmax decreases with age, whereas in women it is not influenced by age[92] Normal women have a higher flow rates for a given voided volume than age matched men. It is likely related to lower outlet resistance.

Normal values for Qmax are given in the table 6 below

Table 6.Normal values for uroflowmetry [93]

Gender	Age(years)	Peak Flow rate(ml/sec)
Males	<40 40-60 >60	>22 >18 >13
Females	<50 >50	>25 >18

2. Chance.

It has been documented that 40% of men have a difference in Q max of at least 2 ml/sec between voids[94]and 20 % of men may have a difference of at least 4 ml/sec[95] .Thus it has been recommended by some that multiple flow rates be recorded to increase the likelihood that a representative flow is achieved[137].

3. Voided volume.

The volume voided probably has the greatest effect on peak flow rate, and it is generally accepted that voided volumes of less than 150 ml generate inaccurate flow patterns and parameters[96,97.] The third International Consultation on Benign Prostatic Hypertrophy (1995) recommends that at least 2 uroflow measurements be taken with at least 150 ml voided each time when performing uroflowmetry. The ICS-BPH study mentions that voids of less than 150 ml can provide useful information (particularly in truly obstructed patients) and thus should not be discarded[98].

The initial intravesical volume is the predominant factor affecting Qmax.[87]

18. RESIDUAL URINE [99]

Residual urine [post void residual (PVR) urine] is defined as the volume of fluid remaining in the bladder immediately following the completion of micturition. A post void residue of less than 50 ml is considered normal, and a post void residue of more than 200 ml is considered abnormal. Values between 50 - 200ml requires clinical correlation.[100]

The measurement of residual urine forms an integral part of the study of micturition. However voiding in unfamiliar surroundings may lead to unrepresentative results, as may voiding on command with a partially filled or overfilled bladder.

Residual urine is commonly estimated by the following methods:

(a) Catheter or cystoscope (transurethral, suprapubic).

(b) Radiography (excretion urography, micturition cystography).

(c) Ultrasonics.

(d) Radioisotopes (clearance, gamma camera).

When estimating residual urine the measurement of voided volume and the time interval between voiding and residual urine estimation should be recorded: this is particularly important if the patient is in a diuretic phase. In the condition of vesicoureteric reflux, urine may re-enter the bladder after micturition and may falsely be interpreted as residual urine. The presence of urine in bladder diverticula following micturition presents special problems of interpretation, since a diverticulum may be regarded either as part of the bladder cavity or as outside the functioning bladder. The various methods of measurement each have limitations as to their applicability and accuracy in the various conditions associated with residual urine. Therefore it is necessary to choose a method appropriate to the clinical problems. The absence of residual urine is usually an observation of clinical value, but does not exclude infravesical obstruction or bladder dysfunction. An isolated finding of residual urine requires confirmation before being considered significant. Furthermore the tests should be repeated because the test retest reliability of post void residual measurements is poor [101.]

19. BLADDER OUTLET OBSTRUCTION

This is the generic term for obstruction during voiding and is characterized by increased detrusor pressure and reduced urine flow rate. Bladder outlet obstruction is usually diagnosed by studying the synchronous values of flow rate and detrusor pressure.

There are no universally accepted urodynamic criteria for the diagnosis of female bladder outlet obstruction; although some have defined it based on urodynamic parameters.[102] Bladder outlet obstruction in women is an infrequently diagnosed urological condition for several reasons. Often it is not suspected .Women have fewer reported classic obstructive symptoms, like poor flow, hesitancy and stranguria, than men, probably in part because they are frequently poor historians with respect to the force of the urinary stream, since they void in private and have little opportunity to compare voiding patterns. Women [103,104] commonly present with irritative symptoms of urinary frequency, urgency, urge incontinence and recurrent urinary tract infections [105,106]

As there are no universally accepted urodynamic criteria for the diagnosis of female bladder outlet obstruction, others have used Urodynamic Parameters in an attempt to define it. [105-107] Normograms for diagnosing bladder outlet obstruction in men, cannot be applied to women. Voiding dynamics are different in women, as many void with low detrusor pressure or by relaxing pelvic floor muscles. Some women by habit augment voiding by abdominal straining. Since

normal voiding detrusor pressure is significantly lower in women than in men, it is reasonable that voiding pressures used to define obstruction would also be different. Carr et al highlighted the difficulties of diagnosing female bladder outlet obstruction based on history, physical examination and common diagnostic tests [108] Therefore, a high index of suspicion and better criteria to define obstruction in women are needed so that clinicians can accurately diagnose and treat the different causes of female bladder outlet obstruction. Chancellor et al has stated that conceptually bladder outlet obstruction may be defined by a detrusor contraction of adequate magnitude, duration and speed, and a low urine flow. [88]

20. BLADDER DYSFUNCTION IN DIABETES MELLITUS

Bladder dysfunction has been recognized as a frequent complication of diabetes mellitus, and has been characterized by impaired bladder sensation, increased bladder capacity and decreased bladder contractility, resulting in increased residual urine, urinary retention or overflow incontinence [109] .

Experimental diabetic animals similarly exhibited bladder dysfunctions, such as increased threshold volume for reflex bladder contraction and altered detrusor contractility [110].The cystopathic findings in diabetic animals were reportedly associated with changes at various levels, including bladder innervating sensory and autonomic pathways and/or the detrusor muscle. [111] Since clinical studies revealed that diabetic neuropathy, such as gastro paresis, abnormal sweating or orthostatic hypotension, was often found in patients with diabetic cystopathy, it has been generally admitted that peripheral neuropathy has an important role in

diabetic cystopathy. [112] However, the underlying mechanisms inducing bladder dysfunction in diabetes remain controversial.

The normal value for bladder sensation or capacity varied among studies. [113-116] .Bladder dysfunctions was found in 36% of 53 patients investigated when it was defined as an increase in bladder capacity to more than 400 ml. with a flat trace on cystometrography according to the criteria proposed by Kahan et a1. [113] Using the criterion that bladder capacity exceeding 500 ml. was regarded as abnormal [116,117]. 32% of patients in one study had diabetic cystopathy. Thus calculated incidences are not different from the 30 to 80% rates in other clinical studies. [79] Frimodt-Moller first reported detailed characteristics of bladder dysfunction, such as loss of bladder sensation and increased bladder capacity, in unselected diabetic patients. [114] In that series diabetic cystopathy was characterized as loss of sensation detected by elevated electrical bladder perception threshold, and it was found in 38% of 100 unselected diabetic patients.

A short history or early stage of diabetes does not exclude the existence of diabetic cystopathy, since bladder dysfunction was observed in patients with diabetes for less than 12 months, no retinopathy or treatment by diet only[118]. The same study from Japan also demonstrated presence of bladder dysfunction in patients without voiding symptoms. Kaplan et al reported that the etiology of voiding dysfunction in diabetic patients with persistent voiding symptoms was attributable not only to classic diabetic cystopathy but also to other

pathophysiological conditions, including bladder outlet obstruction or detrusor hyperreflexia[79].

Autonomic neuropathy detected by the sympathetic skin response coexisted with bladder dysfunction in a significant percentage of diabetic patients. It has been demonstrated that the sympathetic skin response is a simple and valuable test to subjective symptoms alone [118.]In conclusion bladder dysfunction is observed in diabetic patients with and with out subjective voiding symptoms when examined urodynamically.

21. DIABETIC CYSTOPATHY

Diabetic cystopathy is thus a chronic complication of diabetes which is insidious in onset, characterized by increased length of time between voiding .It has received less attention as compared to diabetic nephropathy although it affects day-to-day life. Prevalence is estimated to be between 32% to 45%.[109, 119]

The classic triad of bladder symptoms associated with Diabetic Cystopathy (DC) includes decreased bladder sensation, increased bladder capacity, and impaired detrusor contractility[103] with resultant increased post void residual (PVR) urine [78]. Increased PVR leaves the individual prone to urinary tract infections (UTIs), a common cause of acute confusion and functional decline in older adults. A possible link between deterioration of renal function and chronic asymptomatic bacteriuria in individuals with diabetes has been postulated.[4]

Increasingly, diabetic cystopathy is described as a manifestation of autonomic neuropathy, [119,120] although some believe it also represents peripheral somatic

neuropathy. [121] Several classification systems for diabetic neuropathy have been suggested, but none has included specific lower urinary tract function. Greene, Stevens, and Feldman[122] proposed that genitourinary neuropathy fits within the autonomic neuropathy category, along with sudomotor, cardiovascular, and gastrointestinal neuropathies. Autonomic neuropathies are serious and irreversible complications of diabetes.

Mechanism of diabetic cystopathy

Autonomic neuropathies in diabetes result in axonal degeneration, demyelination, and fiber loss. Hyperglycemia has been implicated as a primary contributor to development of neuropathic complications. Tight control of blood glucose decreases long-term neurological and microvascular complications of diabetes, [123] but the precise relationship of glycaemic control and duration of diabetes to diabetic cystopathy is not known. One possible mechanism of glucotoxicity in nervous tissue is increased polyol pathway activity in which accumulations of sorbitol and fructose induce damage. The exact mechanism of damage has not yet been elucidated. [124,125]

Other possible contributors to diabetic nerve damage include immune mechanisms, microvascular insufficiency, deficiency of growth factor, and decreased expression of laminin, a glycoprotein important in nerve regeneration.[121]

Because diabetic cystopathy is a manifestation of autonomic neuropathy, screening for other signs of autonomic dysfunction may be included, particularly

heart rate and orthostatic hypotension assessment measured by blood pressure while the patient is lying and standing. It is not clear whether cardiovascular autonomic neuropathy occurs with or progresses at the same rate as diabetic cystopathy, but the presence of cardiovascular dysautonomia may identify other problems that need to be addressed. Because one of the hallmarks of diabetic cystopathy is an increase in residual urine, the PVR should be measured either by portable ultrasound or in-and-out catheterization. Ideally, PVR should be measured within minutes of voiding. Norms for acceptable levels of PVR have not been established. One suggested normal range in the older adult is between 50 mL and 150 mL. [126]

Little research has been published to guide practice in diabetic cystopathy management. Evidence is modest at best for all interventions except glycaemic control. Preventing further diabetes associated neuropathy is an important goal in modifying or eliminating risk factors. Other management goals include symptom relief, infection prevention, renal function maintenance, continence, and adequate bladder emptying. [78]

Table 7 . Management strategies for diabetic cystopathy [127]

Glycaemic control	Diet, exercise, weight loss Oral glucose lowering agents Insulin stimulators (secretagogues) Sulfonylurea Meglitinides Insulin sensitizers Biguanides Thiazolidinediones Alpha glucosidase inhibitors Insulin
Voiding Strategies	Scheduled toileting Follow up PVR measurement needed to assess bladder emptying Double voiding Bladder expression Use only if urodynamics demonstrate no vesicoureteral reflux
Catheterization	Intermittent catheterization (if voiding strategies ineffective) Indwelling catheterization (last resort)
Nocturnal polyuria	Fluid management: avoid caffeinated beverages at night, take most of fluids during the day Empty bladder before going to bed

Advising patients to void every two to four hours during the day and to use a double voiding technique may improve bladder emptying, improve continence, and minimize risk of infection. Because diabetic cystopathy is of gradual onset, it may be useful to encourage the diabetic client to begin this habit even if the PVR is below 150 mL. Double voiding involves attempting to empty the bladder by staying on the toilet and trying to void more than once with each trip to the toilet. Elders with cognitive impairment might need supportive cuing from caregivers to carry out the strategy. These noninvasive strategies are worth trying, although their effectiveness has not been studied. Teaching these strategies should be followed with periodic measurement of PVR in patients with elevated residual urine to ensure that adequate bladder emptying is achieved. No effective medications currently are available to assist with bladder emptying in diabetic cystopathy. Bethanechol, a parasympathomimetic agent, has been used with inconsistent results. [128] Research on agents such as aldose reductase inhibitors, which inhibit the accumulation of sorbitol and fructose to potentially improve neuropathy, advanced glycosylation end product, and neurotrophic factors may lead to future treatment options. [128]

4. MATERIALS AND METHODS

Setting

107 older diabetic women who satisfied the inclusion criteria were recruited from the outpatient clinics of the Department of Medicine and the Department of Endocrinology of the Christian Medical College Hospital Vellore, a 2200 bedded tertiary care teaching hospital in South India.

Duration of Study

October 2007 to August 2008.

Inclusion criteria

Female subjects were included in the study if they were ambulant, had Type 2 diabetes mellitus, were above 50 years of age and gave written voluntary consent to take part in the study.

Exclusion criteria

1. Patients with features of lower urinary tract infection (i.e: dysuria with increased frequency or dysuria with urgency or dysuria with fever) were excluded.

2. Patients who were on any antibiotics in the preceding two weeks prior to giving the urine sample were excluded.

3. Subjects who were unwilling to participate voluntarily were excluded.

Ethical Approval

The study had the approval of the hospital Medical and Ethical Committee for research.

Study Design

The study was a cross-sectional descriptive study on asymptomatic bacteriuria in elderly diabetic women attending the Medicine clinics or Endocrine clinic in our centre.

Sample size

Sample size [n] for this descriptive study was calculated by using the following formula

$\mathbf{[n = 4pq / d^2]}$ = 4 x 18 x 82 / 8 X 8 = 5904 / 64 = 92.

Where n=sample size, p=prevalence in %, q=100-p, d= precision.

The desired sample size calculated with a precision of 8% was 92 older diabetic women assuming a prevalence of asymptomatic bacteriuria of 18% in elderly diabetic women.

Study Protocol

107 eligible subjects who satisfied inclusion criteria answered questions to provide the information to fill up a structured questionnaire regarding social, demographic and medical variables. The following features were looked into. The subjects were compared as regarding the presence of microvascular and macrovascular risk factors. They were also compared as for their physical indices and biochemical correlates. (The questionnaire used is attached -**Appendix1**).

They then provided a midstream clean catch sample for purpose of doing urine culture. Those who gave the urine culture sample subsequently went and did uroflowmetry. They also got their post void residual urine volume checked to look for any features of lower urinary tract obstruction or cystopathy.

Uroflometry;

Uroflowmetry was measured by voiding into an uroflowmeter - Urodyn 1000 DANTEC Type 22 G02 which used an uroflow transducer from a rotating drum.

Post void residual urine:

Post void residue was measured by Merlin Ultrasound Model 1101 B-K medicals which used the following formula to calculate the residual urine volume.

V=L.H.W.F

Where L=length,

H=Height,

W=Width,

F=factor (0.53 for bladder)

Urine culture:

Urine was read for growth after incubating at 32 degrees Celsius for 24 hours on blood and McConkey agar. The urine cultures that grew more than 10^5 colonies /ml were considered as asymptomatic bacteriuria.

Definitions:

The following were the cut offs taken for defining the groups:

1. Definition of diabetes mellitus:-Diabetes was assumed for any patient who was on oral hypoglycaemic agents /insulin or any subject fulfilling American Diabetic Association criteria for Diabetes mellitus[20, 21] —

The diagnosis of diabetes was confirmed on a subsequent day by measuring any one of the three criteria.

Fasting ≥ 126mg% (Fasting is defined as no calorie intake for at least 8 hours)

Or 2 hours Postprandial glucose ≥ 200mg%

Or Symptoms of diabetes plus Random Blood Glucose≥200mg%

2. Glycaemic control: - HbA1c <7- was taken as good control

3. Dyslipidemia:-

- If Cholesterol was >200mg/dl

Or Triglycerides was >150mg/dl

Or HDL was <40 mg/dl

Or LDL was >100 mg/dl

4. Body mass Index: - defined as

a) Underweight if BMI was less than 18 kg/m2

b) Normal if BMI was between 19 and 24 kg/m2

c) Overweight if BMI was between 25 and 29 kg/m2

d) Obese if BMI was more than 30 kg/m2

5. Peripheral neuropathy:-

Neuropathy was defined as per the international consensus meeting on the outpatient diagnosis and management of Diabetic neuropathy as “the presence of symptoms and/or signs of peripheral nerve dysfunction in people with diabetes after the exclusion of other causes” [22].

It was taken as present If Monofilament threshold >/= 4gm, in either of the feet- If done by biothesiometer threshold was >/= 25 mV

Light touch sensation was tested using 2gm, 4gm and 10 gm Semmes-Weinstein monofilaments over metatarsal head/ ball of the great toe (while testing; only mild pressure was applied so that the filament was not bent). Loss of sensation over 2gm was considered as peripheral neuropathy in the lower limbs. Loss of protective sensation in the lower limb is indicated by 10 Gms loss of sensation. The patient is asked to say “yes” each time he or she feels the filament. Failure to feel the filament at four of ten sites is 97% sensitive and 83% specific for identifying loss of protective sensation. This method has sufficient reproducibility, when used as a screening test for diabetic foot ulcerations.

Quantitative Sensory Testing was done by using a Biothesiometer.This provides a quick and reliable assessment of vibration thresholds, which gives an

objective measure of the progress of diabetic peripheral neuropathy. A value above 25V was taken as evidence of neuropathy.

However, when a biothesiometer was not available detection of impairment of vibration sense was done using tuning fork (128 Hz).

6. Nephropathy[115]:-

-Microalbuminuria was present if the urine microalbumin was between 30 and 300 microgm/mg of creatinine or 30- 300 mg/day in a 24 hour urine collection.

-macroproteinuria– If urine microalbumin >300 microgm/mg of creatinine or 24 hour urine protein was more than 500mg/24 hours.

7. Retinopathy:- Present or absent as confirmed by an Ophthalmologist .The diagnosis was made in the presence of microaneurysms, dot and blot hemorrhages and evidence of clinically significant macular edema, or any patient who LASER/ intervention for retinal detachment/ vitreous hemorrhage.

8**.** Cardiovascular disease: - Any of the following features were taken:

a) Past history of acute coronary syndrome

b) Stable angina

c) History of PTCA/ Coronary artery bypass grafting

d) Tread Mill Test (TMT) positivity

9. Cerebrovascular disease: - Any of the following features:

a) History of transient ischemic attack/ stroke

b) Carotid stenosis- either carotid bruit or Doppler proven

10. Peripheral vascular disease: - Any of the following features:

a) Absent peripheral pulses

b) Claudication pain

c) History of gangrene/ amputation

11. Renovascular disease: - Any of the following features:

a) Renal bruit

b) Doppler evidence of renal artery stenosis

12. Obstructive uropathy /cystopathy:-This was defined as per the standard urologic terminology of the International Continence Society guidelines .Abnormal post void residual urine was defined as PVR more than 10% of the voided volume measured by ultrasound. Abnormal uroflowmetry was defined as the presence of Peak urine flow less than 20 ml/sec measured by an uroflowmeter.

13. Asymptomatic bacteriuria:-Defined as the presence of at least 10^5 colony forming units /ml of 1 or 2 of the same microorganism in a culture of clean voided midstream urine from a patient without fever or a symptoms of a urinary tract infection.

STATISTICAL ANALYSIS OF DATA

The prevalence of asymptomatic bacteriuria was calculated. Prevalence of diabetic cystopathy /obstructive uropathy was calculated among those with and without asymptomatic bacteriuria. Analysis was done among the group with asymptomatic bacteriuria as compared with those without asymptomatic bacteriuria to calculate the relative risk, odds ratio, and 95%C.I for suspected risk factors like elevated HbA_{1C}, length of diabetes, presence of macrovascular complications, past history of urinary tract infection etc. Univariate analysis of individual risk factors was performed for the final analysis. The statistical software SPSS 16.0 for Windows was used for statistical calculations.

5. RESULTS

A total of 107 diabetic women patients were evaluated for the prevalence of asymptomatic bacteriuria between October 2007 and August 2008.All were diabetics who attended the diabetic endocrine out patient clinic or the Medicine out patient clinics at the Christian Medical College Hospital (CMCH)Vellore. All of them were evaluated for diabetic co morbidities and complications-both microvascular and macrovascular.Of these 78 patients had given urine for culture to look for asymptomatic bacteriuria. Among them 61 went on to do the uroflowmetry to look for evidence of obstructive uropathy .Only 57 completed the post void residual urine estimation which was to look for diabetic cystopathy.

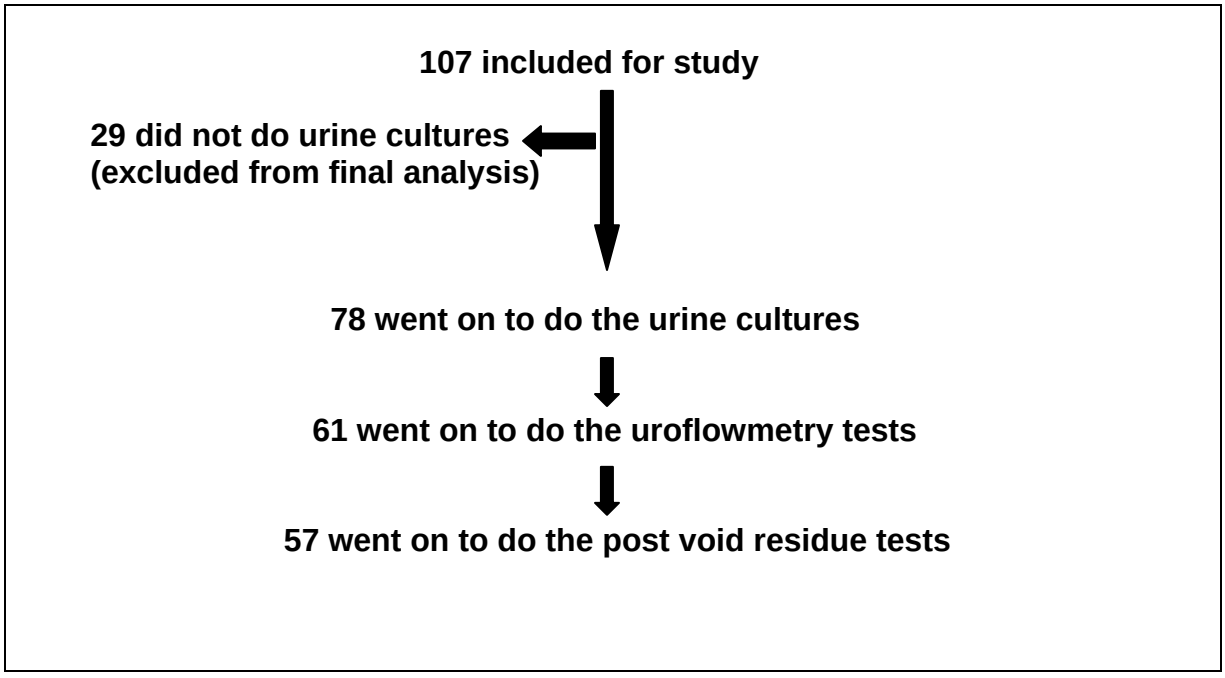

Figure 3. Flow chart showing patient recruitment

Table 8. Characteristics of subjects who gave urine for culture

Patient characteristics	**n is either MEAN +/-SD or number (%)**
Age	59.12(+/- 6.74)
Duration of diabetes (years)	10.13(+/- 7.5)
HbA_{1C}	8.41(+/- 1.70)
Fasting blood sugar <110	15(19.5%)
Post prandial blood sugar<140	11(14.3%)
BMI (Kg/M^2)	26.10(+/- 3.85)
Insulin use	27(34.6%)
Past history of UTI	7(9%)
Functionally dependent	3 (3.9%)
Past urinary catheterisation	17(21.8%)
Past renal stones	3(3.8%)
Presently have urinary incontinence	17(22.1%)
Significant urine culture	13(16.6%)
Escherichia coli in positive urine culture	11(84%)

1. AGE:

The mean age of the subjects was 59.12 years(+/- 6.742) with a range from 50 to 76 years. 58% of the subjects fell within the age groups of 50-59 years,26% between the age groups of 60-69 and 8% were 70 years or older. All the subjects with asymptomatic bacteriuria were between the age groups of 50-70 years. **Figure 4** shows the age wise distribution of the subjects.

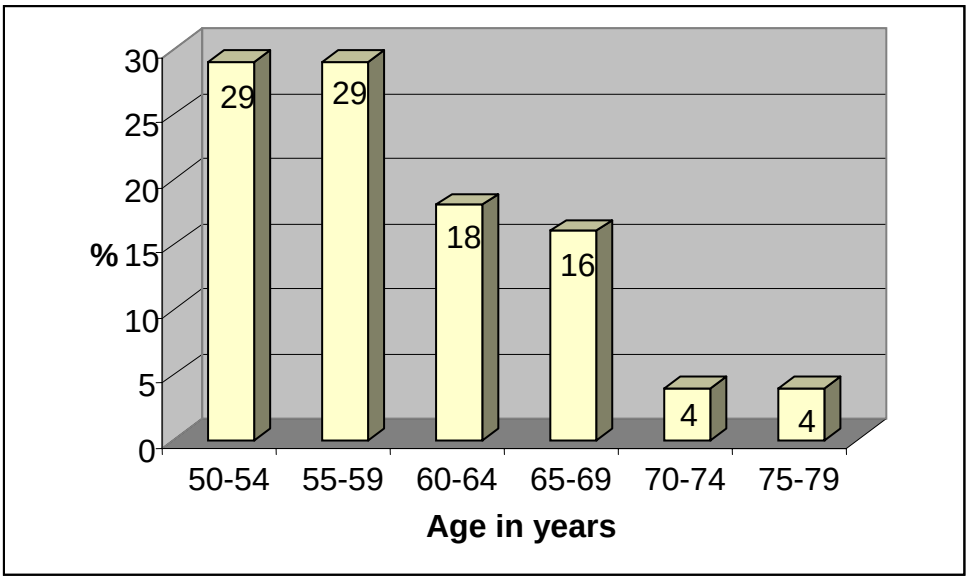

Figure 4. Age distribution of the subjects

2. Duration of diabetes (years):

The duration of diabetes ranged from 0.25 years to 30 years with a mean duration of 10.08 years (+/- 7.64)

3. HbA_{1C}:

The HbA_{1C} ranged between 6gm% and 13gm% with a mean of 8.24gm% (+/- 1.56),14.3%(9 out of 63) of the subjects had a HbA_{1C} which was <7gm% indicating good glycaemic control. 15.9% (10 out of 63) of the subjects had a poor glycaemic control with HbA_{1C} of =/>10gm%. The breakdown of the HbA_{1C} among those with asymptomatic bacteriuria is given in the table below.

Table 9. Glycaemic control in relation to asymptomatic bacteriuria

HbA1c	Significant urine culture	
	absent	present
<7 gm%	8(15.4%)	1(9.1%)
7-9.99 gm%	38(73.1%)	6(54.5%)
>9.99 gm%	6(11.5%)	4(36.4%)

The HbA_{1C} levels and the risk of developing ASB was not significant

(Fisher's Exact Test =0.135).

4. BMI (Kg/M^2):

The BMI ranged from 16.8 to 34.2 Kg/m^2.The mean BMI was 26.10 Kg/m^2 (+/- 1.70). 34 %(25) of the subjects had a BMI between 19-25 Kg/m^2. 4 %(3) of the subjects were underweight.47 %(35) of the subjects were overweight .15 %(11) of the subjects were obese.

5. Medication.

6% (5) of the patients were on insulin only and 66% (51) were on oral hypoglycaemic agents (OHA's) only. 28% (22) were on both OHA's and insulin. There were no patients exclusively on diabetic diet. Table 10 shows the diabetic treatment of the screened subjects.

Table 10. Pattern of anti diabetic medication use

MEDICATION	**%**
OHA ONLY	66
INSULIN ONLY	6
OHA&INSULIN	28

6. Urinary cultures positive for asymptomatic bacteriuria:

The prevalence of asymptomatic bacteriuria detected was 16.7% (13 out of 78).

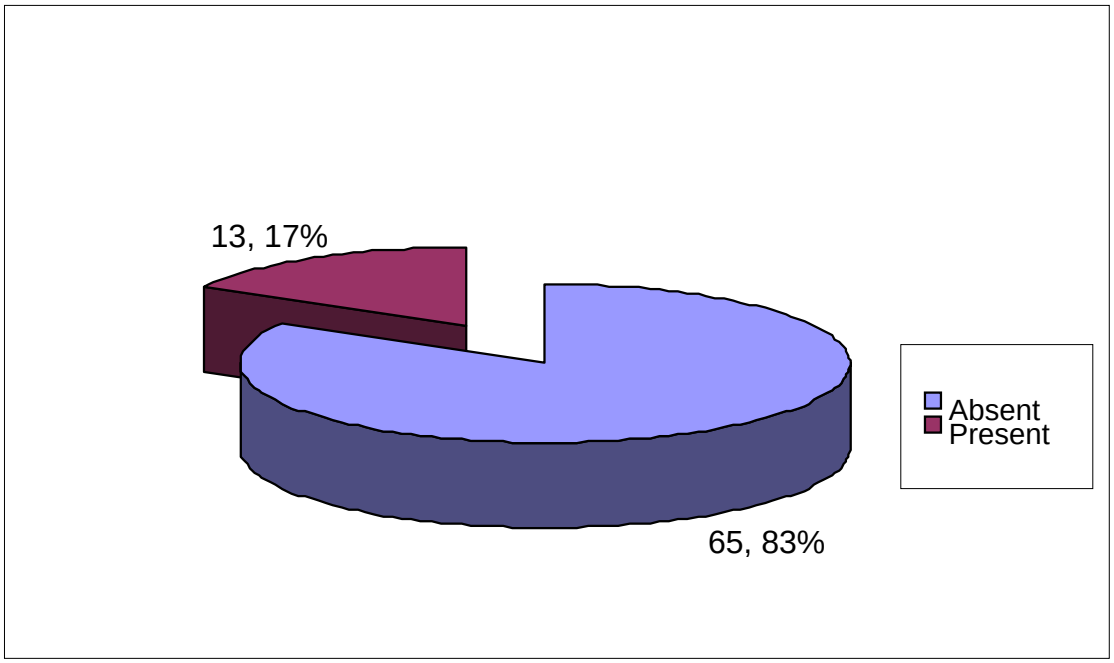

Figure 5. Prevalence of asymptomatic bacteriuria

The commonest organism isolated was Escherichia coli among the 13 people with significant growth on urine culture (asymptomatic bacteriuria).Of them Escherichia coli was 84% (11), Proteus 8 %(1) and Citrobacter diversus 8 %(1)

Table 11. Diabetic co morbidities and complications

Dyslipidemia	26(46.2%)
Serum creatinine	0.88(+/- 0.22)
Normoalbuminuria(<30 mg)	25(42.4%)
Microalbuminuria (30-300mg)	30(50.8%)
Macroalbuminuria(>300mg)	4(6.8%)
Nephropathy	34(57.6%)
Peripheral neuropathy	23(31.5%)
Autonomic neuropathy	1(1.4%)
Retinopathy	12(15.4%)
Macrovascular complications	10(12.8%)
Ischaemic heart disease	9(11.5%)
Cerebrovascular disease	0(0%)
Renovascular disease	0(0%)
Peripheral vascular disease	1(1.3%)

DIABETIC COMORBIDITIES AND COMPLICATIONS

1. Dyslipidemia:

46.2 %(26) had dyslipidemia

2. Serum creatinine:

The serum creatinine ranged between 0.6 to 1.9 mg/dl. The mean serum creatinine was 0.88mg/dl (+/-.225).

3. Microvascular complications: 15.4 %(12) had retinopathy, and 31.9% (23) had neuropathy.57.6% (34) had nephropathy. This is shown in the Figure 6.

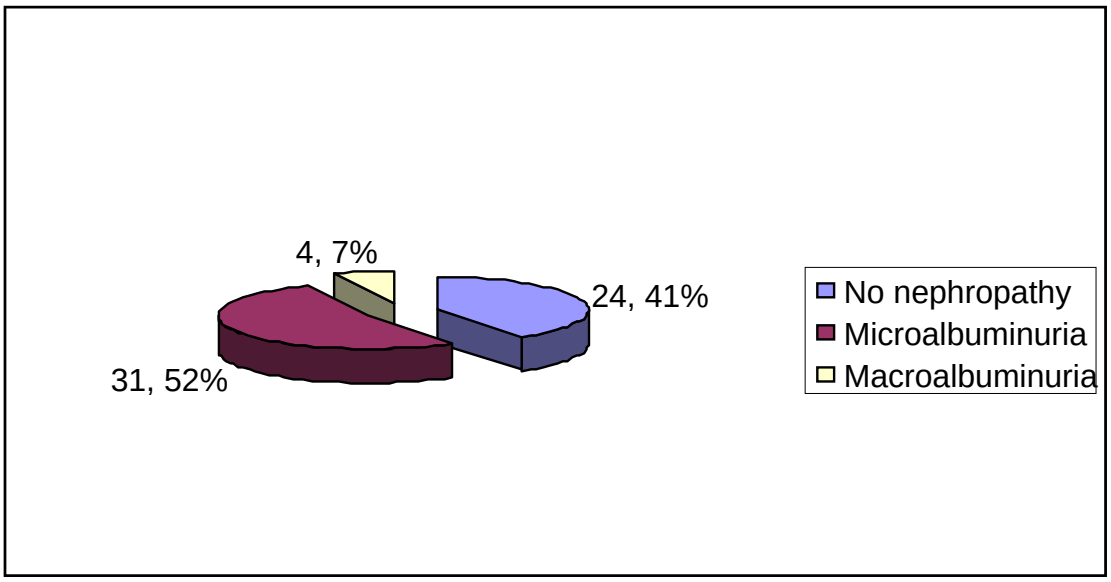

Figure 6.Renal status of the subjects

4. Macrovascular complications:

The prevalence of ischaemic heart disease was 11.5 %(9).The prevalence of peripheral vascular disease was 1.3 %(1).The prevalence of renovascular disease was 0 in the studied population. The prevalence of cerebrovascular disease was 0 in the studied population.

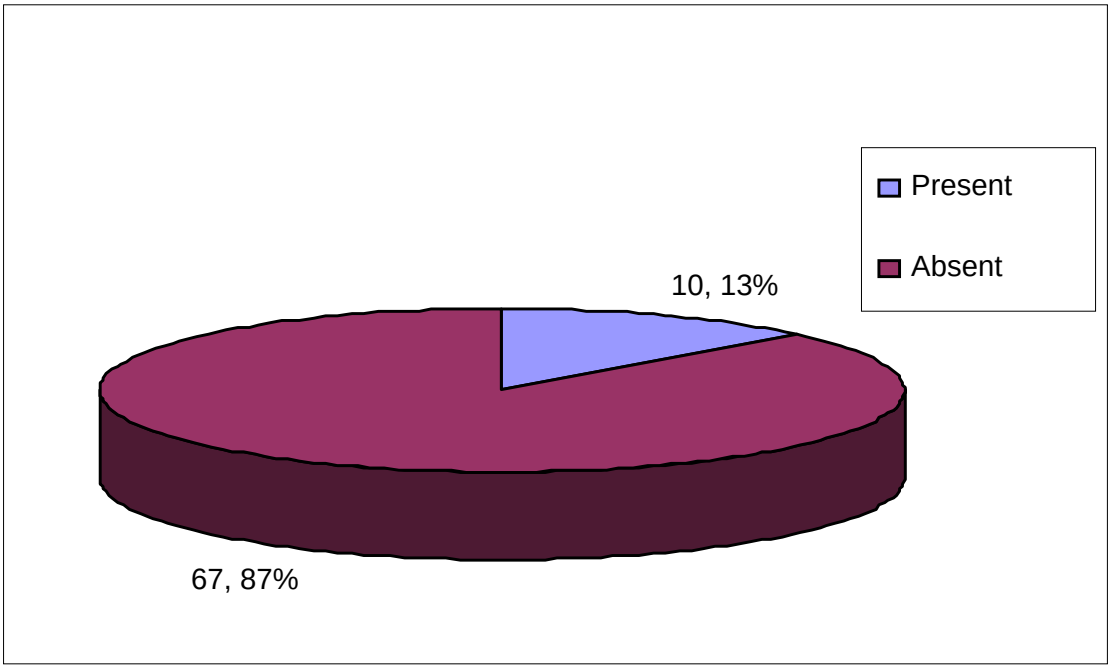

Figure 7. Prevalence of macrovascular complications

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Table 12. Characteristics of the PVR and Uroflowmetry

Patient characteristics	**n is either MEAN +/-SD or number (%)**
Post void residue (PVR) < 50 ml	42(73.7%)
Post void residue (PVR) 50-100 ml	12(21.1%)
Post void residue (PVR) > 100 ml	3(5.3%)
Mean Post void residue (PVR)	39.02(+/- 39.13)
Mean peak urinary flow rate(Qmax)	22.87(+/- 10.46)
Qmax <10ml/sec	1(1.6%)
Qmax 10-20ml/sec	30(49.2%)
Qmax >20ml/sec	30(49.2%)

Uroflowmetry and PVR.

The prevalence of abnormal peak urinary flow rate on uroflowmetry (Q max) was 50.8 %(31 out of 61).The prevalence of abnormal Q max during uroflowmetry among those with asymptomatic bacteriuria was 63.6% (7 out of 11). The mean Qmax was 22.87+/-10.46. People with lower Q max especially < 10 ml/sec had a 1.154 times greater risk estimate of having asymptomatic bacteriuria as compared with those with Qmax >20 ml/sec which was statistically significant (95% C.I=1.003-1.328).

The prevalence of abnormal post void residue was 43.6% (24 out of 55).The prevalence of abnormal post void residue was 36.4% among those with

asymptomatic bacteriuria (4 out of 11). The mean post void residue was 39.02 ml +/-39.13.There were 42 (73.7%) diabetic women with PVR less than 50 ml. There were 12 (21.1%) diabetic women with PVR between 50 ml-100ml and 3 (5.3%) diabetic women with PVR more than 100 ml. This is shown in the **Figure 8**

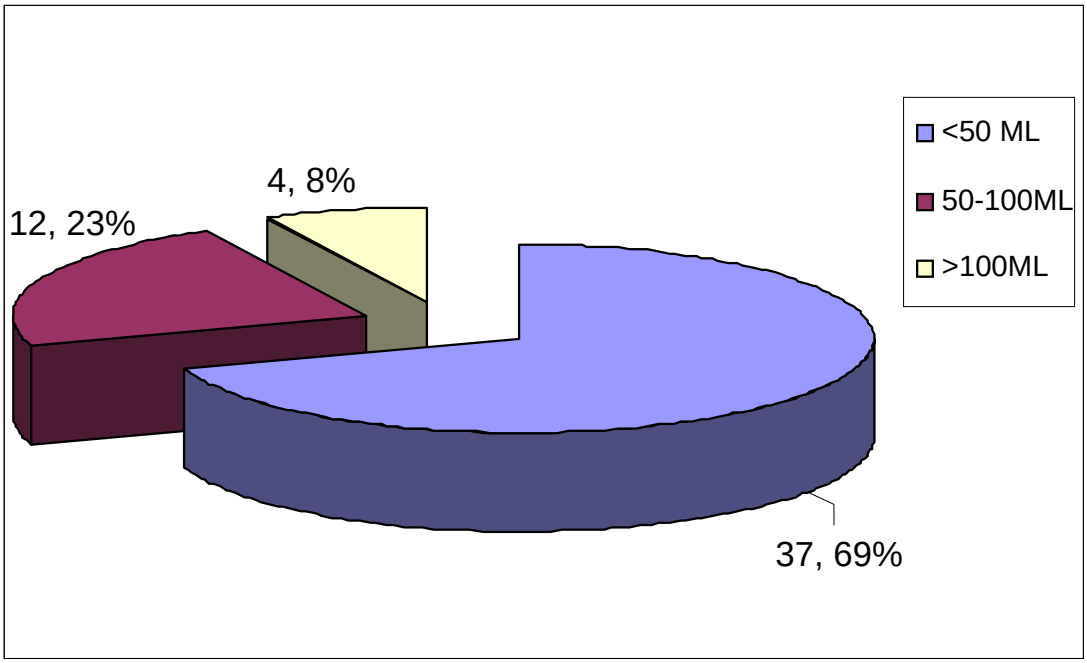

Figure 8. Post void residual urine volume

Prevalence of either abnormal PVR or Qmax among all the study subjects was 64.5 %(40 out of 62).Prevalence of either abnormal PVR or Qmax among those with asymptomatic bacteriuria was 60.5% (6 out of 10).

Table 13 .Profile of subjects with asymptomatic bacteriuria

Significant urine culture	Minimum	Maximum	Mean	Std. Deviation
Age	53	68	59.46	5.517
HbA1c	6	13	9.19	2.198
Duration(years)	.50	25.00	10.3462	7.08691
Creatinine(Mg/dl)	.80	1.70	.9333	.26054
Body Mass Index	16.8	34.2	26.167	4.8331
PVR(ML)	10	49	19.27	11.001
Q MAX(ML/SEC)	10.10	47.50	22.3000	11.68623
Valid N (listwise)				

The baseline characteristics of the people with and without asymptomatic bacteriuria was similar except with respect to post void urine residue (PVR) as seen in Table 6 .which was not statistically significant.
(Risk estimate 0.68, 95% CI=.175-2.683)

Table 14. Comparison of subjects with and without asymptomatic bacteriuria

Characteristics	No ASB		Significant urine culture(ASB)	
	Mean	Std. Deviation	Mean	Std. Deviation
Age(Years)	59.05	6.996	59.46	5.517
HbA1c	8.24	1.560	9.19	2.198
Duration(years)	10.0808	7.64203	10.3462	7.08691
Creatinine (Mg/dl)	.8750	.21763	.9333	.26054
BODY MASS INDEX(Kg/M2)	26.095	3.6819	26.167	4.8331
PVR(ML)	43.74	41.960	19.27	11.001
Q MAX(ML/SEC)	23.0020	10.29796	22.3000	11.68623
Valid N (listwise)				

Table 15 . Risk factors for asymptomatic bacteriuria in women with Type 2 diabetes mellitus.

Risk factors N **General characteristics**	**ASB absent No(%)**	**ASB present No(%)**	**Odds Ratio**	**95% C.I**
Age less than 60 years	43	8	1.22	.357-4.179
Age more than 60 years	22	5		
Duration of diabetes <10 years	43(81.1)	10(18.9)	.586	.146-2.351
Duration of diabetes >10 years	22(88)	3(12)		
UTI in the previous year (No)	62(87.3)	9(12.7)	.738	.616-.884
UTI in the previous year(Yes)	3(42.9)	4(57.1)		
BMI (Kg/m^2) < 25	24(85.7)	4(14.3)	1.263	.343-4.656
BMI (Kg/m^2) >/=25	38(82.6)	8(17.4)		
HbA_{1C} <7	8(88.9)	1(11.1)	5.33	.468-60.797
HbA_{1C} =/>10	6(60.0)	4(40.0)		
Drugs(No Insulin use)	47(92)	4(8)	5.875	1.606-21.494
Drugs(Insulin use alone or as combination with OHA)	18(66)	9(34)		

Table 16. Risk factors for diabetic comorbidities and complications

Risk factors N	ASB absent No(%)	ASB present No(%)	Odds Ratio	95% C.I
Dyslipidemia absent	28(75.7)	9(24.3)	2.571	.713-9.270
Dyslipidemia present	32(88.9)	4(11.1)		
Normal Serum creatinine	55(83.3)	11(16.7)	5.00	.290-86.128
Abnormal Serum creatinine	1(50)	1(50)		
Retinopathy absent	43(89.6)	5(10.4)	4.3	.944-19.582
Retinopathy present	8(66.7)	4(33.3)		
Peripheral neuropathy absent	41(83.7)	8(16.3)	1.079	.289-4.030
Peripheral neuropathy present	19(82.6)	4(17.4)		
Nephropathy Absent	23(92)	2(8)	3.538	.681-18.387
Nephropathy Present	26(76.5)	8(23.5)		
Microvascular complications (No)	10(83.3)	2(16.7)	1.184	.220-6.374
Microvascular complications (Yes)	38(80.9)	9(19.1)		
Macrovascular complications (No)	58(86.6)	9(13.4)	4.296	1.011-18.260
Macrovascular complications(Yes)	6(60)	4(40)		

Table 17. Risk factors Uroflowmetry and PVR

Risk factors N	ASB absent No(%)	ASB present No(%)	Odds Ratio	95% C.I
Post void residue<50 ml	31(73.8)	11(26.2)	Risk Estimate .738	.616-.884
Post void residue>50 ml	15(100)	0(0)		
Normal Post void residue (<10% of voided volume)	23(76.7)	7(23.3)	.329	.036-3.034
Abnormal Post void residue (>20% of voided volume)	10(90.9)	1(9.1)		
Normal Qmax(>20ml/sec)	26(86.7)	4(13.3)	Risk Estimate 1.154	1.003-1.328
Abnormal Qmax (<10 ml/sec)	1(100)	0(0)		

Diabetics with macrovascular complications had 4.2 higher risk of developing ASB as compared to patients without macrovascular complications of diabetes which was statistically significant (95%CI 1.011-18.260).

Subjects taking insulin had a 5.87 times the odds of developing ASB as compared to those without ASB. This was statistically significant ((95% CI = 1.61-21.5).

Patients with HbA_{1c} >10gm% had 5.33 times higher risk of having ASB than patients with HbA_{1c} <7gm% .This figure was however not statistically significant (95%C.I =0.46-60.797).

Patients with duration of diabetes >10 years had a 2.37 times higher risk of having ASB than patients with a duration of diabetes <5 years. This figure was however not statistically significant (95%, C.I =0.447-12.571).

There was no significant association for asymptomatic bacteriuria with age, duration of diabetes, HbA_{1c}, body mass index , lipid status, creatinine values, nephropathy, neuropathy, microvascular complications, peripheral vascular complications, heart disease, past history of urinary tract infections, past catheterization , urinary incontinence, past renal stones, peak urinary flow rates and post void residue urine.

6. DISCUSSION

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A total of 107 older diabetic women were screened for the study of which 78 followed up to do the urine cultures.13 patient's had significant urine cultures with colony counts greater than greater than 10^5 colonies/ml. The overall prevalence of asymptomatic bacteriuria (ASB) was 16.7 %,(13 out of 78). This prevalence of ASB was similar to what was described by Bonadio et al in 2004[132].

Geerlings et al in 2000 reported a prevalence of 26%.[55].Our study was thus similar to earlier studies of diabetic women with the prevalence ranging from 8–26% [4, 12,129,130].

Diabetic subjects taking insulin had 5.87 times higher odds of developing ASB as compared to those not on insulin. This was statistically significant ((95% CI = 1.61-21.5). This finding is similar to what was found by Bokyo et al in 2005 [51]. Women taking insulin were mainly at higher risk, possibly because of more severe diabetes since the use of insulin may be a marker of disease severity[142].

Subjects with macrovascular complications had 4.2 higher odds of developing ASB as compared to diabetic women without macrovascular complications. This result was statistically significant (95%CI 1.011-18.260).

Prevalence of abnormal Q max during uroflowmetry among those with asymptomatic bacteriuria was 70% (7 out of 10). Diabetic subjects with a lower peak urinary flow rates (Q max) especially < 10 ml/sec had a 1.154 times greater

risk estimate of having asymptomatic bacteriuria as compared with those with Qmax >20 ml/sec.This result was statistically significant (95% C.I=1.003-1.328). This could probably be indicative of a greater amount of bladder dysfunction which is a long term complication of asymptomatic bacteriuria and diabetes.

Diabetic subjects with retinopathy had 4.3 times the odds of developing ASB as compared to subjects without retinopathy. This figure was almost reaching statistical significance (95% C.I =0.944-19.58).

Diabetic subjects with dyslipidemia had a 2.5 times greater risk of developing ASB as compared to diabetics with no dyslipidemia.This was however not statistically significant. (95% C.I =0.46-60.797).

Diabetic subjects with abnormal serum creatinine had a 2.5 times greater risk for developing ASB as compared to diabetics with normal serum creatinine.This was however not statistically significant. (95% C.I =0.29-86.128).This was unlike what Ishay A et al described in 2006 who found serum creatinine as an independent risk factor for ASB [143] .

Diabetic patients with Nephropathy had 3.5 times risk of getting ASB as compared with patients who had no nephropathy. However this figure was not statistically significant (95% C.I =.681-18.387).

Some studies have shown that a longer duration of diabetes increases the risk of developing ASB [50] while others could not confirm this notion[134-136]. In our study duration of diabetes greater than 10 years as compared to those with diabetes

duration less than 5 years showed a 2.3 times greater risk estimate which was not statistically significant(95% CI=0.447-12.571).

There was a 5.33 times higher odds of patients with HbA_{1c} >10gm% as compared to patients with a HbA_{1c} <7gm% having asymptomatic bacteriuria which was not statistically significant. (95% C.I =0.46-60.797).This is similar to most studies[4, 12, 55,129], but not all[132], which have found no relationship between glycaemic control and ASB.

A variety of potential ASB risk factors have been assessed in previous, mostly small-scale studies with inconsistent results. In these studies there was no significant association for ASB with microvascular complications, vascular complications, heart disease, past history of urinary tract infection, past catheterization, urinary incontinence and renal stones.

Though age is a well known risk factor for bacteriuria in women without diabetes[133] and some studies have shown age as the most important risk factor for ASB in Type 2 diabetes mellitus[55], age had no significant relationship with ASB in our study (Odds=1.22 with 95% CI =0.36-4.18).

In our study Body mass index (BMI) was not associated with any significant association with ASB (Odds ratio=1.26 with 95% CI was 0.34-4.65) .However Geerling et al [55] has proposed a low BMI as a risk factor for ASB.

Chronic complications such as nephropathy and neuropathy have been associated with ASB in type 1 but not with type 2 diabetic patients[11, 129] a pattern that also holds for longer diabetes duration[11]. In some of these studies, a small sample size and restricted number of variables limit the conclusions that could be drawn. We found no significant association between the occurrence of nephropathy or neuropathy and development of ASB.

The prevalence of abnormal post void residue was 36.4% among those with asymptomatic bacteriuria (4 out of 11).There was no significant correlation (Odds ratio=0.329) among the presence of bladder residue and ASB. As found in other studies the presence of peripheral neuropathy did not correlate significantly with bladder residue, and ASB[55,80].

We diagnosed ASB using a single urine culture as it was the most practical and cost-effective way to screen patients routinely. Although the definition of ASB in women conventionally requires two urine cultures taken >24 hours apart, this practice does not improve specificity compared with a single specimen collection[98].

The commonest organism isolated was Escherichia coli (84%) among the 13 women with significant growth on urine culture (asymptomatic bacteriuria).The organism was similar to most other studies [131,132] .The other organisms were Proteus 8%(1) and Citrobacter diversus 8 %(1).

As there is a higher risk of and ASB and acute symptomatic urinary tract infections(UTIs) among post menopausal women[51] with diabetes further adequately powered multicentre intervention studies are, therefore, needed to determine whether active screening for, and prompt antibiotic treatment of, ASB in diabetes is effective to reduce the risk of morbidity from UTIs.

7. CONCLUSION

1. Asymtomatic bacteriuria is a common finding in adults and diabetic women have a higher prevalence of this condition.

2. In our study the prevalence of asymptomatic bacteriuria was 16.7%.

3. There was no significant association between the occurrence of post voidal residual urine (PVR) and asymptomatic bacteriuria.

4. There was no association between asymptomatic bacteriuria and the presence of peripheral neuropathy.

5. Presence of macrovascular complications and the usage of insulin had a significantly increased risk of having asymptomatic bacteriuria.

9. LIMITATIONS

1. One of the drawbacks of the study was the small sample size which would limit the statistical significance of individual risk factors. Multivariate analysis for comparing significant risk factors was not done in view of the small sample size.
2. Only a single urine culture was used in diagnosing asymptomatic bacteriuria due to financial constraints.
3. Community studies would be required with representative women to fully generalize the results to the rest of the community population as the sample population was mainly diabetic women who presented to this tertiary care teaching hospital from the Vellore district of Tamil Nadu.
4. The exact onset of Diabetes cannot be easily determined, since symptoms may remain occult for years[130]. Error in estimating diabetes duration due to this problem is likely to underestimate the associated effects.
5. Due to ethical issues we did not do invasive cystometrogram based pressure flow studies of the people who had significantly abnormal uroflowmetry and post void residual urine abnormal results which could help truly confirm obstructive uropathy and true detrusor dysfunction.
6. Presence of autonomic neuropathy other than postural drop in blood pressure was not measured.

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ANNEXURES 1

QUESTIONNAIRE

1. Name:			2. Age:
3. Address :			
4. Telephone no:		5. Hospital No:	
6. Weight in Kg:	7 .Height in Meters:		8.Body mass index:

9. Are you functionally independent:	YES	NO	
10. Have you had urinary tract infection in the past:	YES	NO	
11. Have you had urinary catheterization in the past:	YES	NO	
12. Have you had renal stones in the past:	YES	NO	
13. Have you had urinary incontinence:	YES	NO	

ABOUT DIABETES: - circle the appropriate response

14. TYPE OF DIABETES :	TYPE 1	TYPE 2	
15. DURATION OF DIABETES IN YEARS:			

MICROVASCULAR & MACROVASCULAR COMPLICATIONS:-circle the appropriate response

16. MEDICATIONS:	OHA	INSULIN		
17.PERPHERAL NEUROPATHY:	paresthesia	sensory loss	motor neuropathy	sensorimotor
18.AUTONOMIC NEUROPATHY: postural drop in blood pressure				
19.DIABETIC RETINOPATHY :	Non Proliferative DR	Proliferative DR	(laser Therapy /CSME)	(Vitreous haemmorhage/Retinal detachment)
20.ISCHAEMIC HEART DISEASE	Stable angina	old MI / ACS	TMT positivity	PTCA /CABG
21.CEREBROVASCULAR DISEASE	TIA	CVA	carotid stenosis	Bruit/Doppler abnormality
22.PERIPHERAL VASCULAR DISEASE	absent pulses	claudication pain	gangrene	amputation
23.RENOVASCULAR	Bruit	Doppler		
24. DYSLIPIDEMIA	PRESENT	ABSENT	If present: Treated (YES/NO)	

INVESTIGATIONS:-

25. FBS:		
26. PPBS:		
27. HbA1c:		
28. S.CREATININE:		
29.TWENTY FOUR HOUR URINE PROTEIN:		MICROALBUMINURIA:
32. URINE CULTURE:		
33.POSTVOIDRESIDUE (PVR)URINE:		
34.UROFLOWMETRY:	Qmax:	Average flow rate:

ANNEXURES 2

ABSTRACT

Title: Asymptomatic bacteriuria in older diabetic women .

Department: Department of Medicine Unit 3 and Geriatrics,

Christian Medical College Hospital, Vellore - 632004.

Name of the candidate: Dr. Sushil Thomas Alexander,

Postgraduate Student,

General Medicine.

Degree: MD (General Medicine)

Name of the Guide: Dr. K. Prasad Mathews

Professor of Medicine,

Department of Medicine Unit 3 and Geriatrics,

Christian Medical College Hospital, Vellore.

Objectives of the study:

To study the prevalence and clinical and laboratory predictors of asymptomatic bacteriuria in older women with Type 2 diabetes.

Methods:

A total of 107 diabetic women ,50 years and above ,who attended the Medicine and Endocrinology outpatient clinic were included in the study .We evaluated risk

factors by interviewing and screening for the presence of asymptomatic bacteriuria in these women .At least 1 uncontaminated urine sample was taken for analysis. Asymptomatic bacteriuria was defined as at least 10^5 colony forming units /ml of 1 or 2 bacterial species from the culture of the midstream clean catch sample from individuals without symptoms of urinary tract infection.

Results:

The prevalence of asymptomatic bacteriuria was 16.7% in Type 2 diabetic women .Risk factors for asymptomatic bacteriuria in Type 2 diabetic women included presence of macrovascular complications ,the use of insulin and the presence of lower peak urinary flow rates. No significant association was associated with age, BMI, duration of diabetes, HbA1c, dyslipidemia, nephropathy, neuropathy and microvascular diabetic complications.

Conclusion

Asymptomatic bacteriuria is a commonly prevalent condition in older women with Type 2 diabetes mellitus .The most common organism cultured was Escherichia coli.